

FOURTH EDITION

Physical Pharmacy

PHYSICAL CHEMICAL PRINCIPLES IN THE PHARMACEUTICAL SCIENCES

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sodium stearate and cholesterol, sodium lauryl sulfate and glyceryl monostearate, and tragacanth and Span. Chun et al.³² determined the hydrophile-lipophile balance of some natural agents and further discussed the principle of mixed emulsifiers.

The type of emulsion that is produced, *o/w* or *w/o*, depends primarily on the property of the emulsifying agent. This characteristic is referred to as the *hydrophile-lipophile* balance, that is, the polar-nonpolar nature of the emulsifier. In fact, whether a surfactant is an emulsifier, wetting agent, detergent, or solubilizing agent may be predicted from a knowledge of the hydrophile-lipophile balance, as discussed in a previous chapter (p. 371). In an emulsifying agent, such as sodium stearate, $C_{17}H_{35}COONa$, the nonpolar hydrocarbon chain, $C_{17}H_{35}$ —, is the *lipophilic* or "oil-loving" group; the carboxyl group, $—COONa$, is the *hydrophilic* or "water-loving" portion. The balance of the hydrophilic and lipophilic properties of an emulsifier (or combination of emulsifiers) determines whether an *o/w* or *w/o* emulsion will result. In general, *o/w* emulsions are formed when the HLB of the emulsifier is within the range of about 9 to 12, and *w/o* emulsions are formed when the range is about 3 to 6. An emulsifier with a high HLB, such as a blend of Tween 20 and Span 20, will form an *o/w* emulsion. On the other hand, Span 60 alone, having an HLB of 4.7, tends to form a *w/o* emulsion.

It would appear, therefore, that the type of emulsion is a function of the relative solubility of the surfactant, the phase in which it is more soluble being the continuous phase. This is sometimes referred to as the *rule of Bancroft*, who observed this phenomenon in 1913. Thus, an emulsifying agent with a high HLB is preferentially soluble in water and results in the formation of an *o/w* emulsion. The reverse situation is true with surfactants of low HLB, which tend to form *w/o* emulsions. Beerbower, Nixon, and Hill³³ suggested an explanation for emulsion type and stability and devised a general scheme for emulsion formulation based on the Hildebrand and Hansen solubility parameters (pp. 224, 225).

Multimolecular Adsorption and Film Formation. Hydrated lyophilic colloids have been used for many years as emulsifying agents, although their use is declining because of the large number of synthetic surfactants now available. In a sense, they may be regarded as surface active since they appear at the oil-water interface. They differ, however, from the synthetic surface-active agents in that (1) they do not cause an appreciable lowering of interfacial tension, and (2) they form a multi- rather than a monomolecular film at the interface. Their action as emulsifying agents is due mainly to the latter effect, for the films thus formed are strong and resist coalescence. An auxiliary effect promoting stability is the significant increase in the viscosity of the dispersion medium. Since the emulsifying agents that form multilayer films around the

droplets are invariably hydrophilic, they tend to promote the formation of *o/w* emulsions.

Solid Particle Adsorption. Finely divided solid particles that are wetted to some degree by both oil and water can act as emulsifying agents. This results from their being concentrated at the interface, where they produce a particulate film around the dispersed droplets so as to prevent coalescence. Powders that are wetted preferentially by water form *o/w* emulsions, whereas those more easily wetted by oil form *w/o* emulsions.

PHYSICAL STABILITY OF EMULSIONS

Probably the most important consideration with respect to pharmaceutical and cosmetic emulsions is the stability of the finished product. The stability of a pharmaceutical emulsion is characterized by the absence of coalescence of the internal phase, absence of creaming, and maintenance of elegance with respect to appearance, odor, color, and other physical properties. Some workers define instability of an emulsion only in terms of agglomeration of the internal phase and its separation from the product. Creaming, resulting from flocculation and concentration of the globules of the internal phase, sometimes is not considered as a mark of instability. An emulsion is a dynamic system, however, and flocculation and resultant creaming represent potential steps toward complete coalescence of the internal phase. Furthermore, in the case of pharmaceutical emulsions, creaming results in a lack of uniformity of drug distribution and, unless the preparation is thoroughly shaken before administration, leads to variable dosage. Certainly, the eye-appeal of an emulsion is affected by creaming, and this is just as real a problem to the pharmaceutical compounder as is separation of the internal phase.

Another phenomenon important in the preparation and stabilization of emulsions is *phase inversion*, which can be an aid or a detriment in emulsion technology. Phase inversion involves the change of emulsion type, from *o/w* to *w/o* or vice versa. Should phase inversion occur following preparation, it may logically be considered as an instance of instability.

In the light of these considerations, the instability of pharmaceutical emulsions may be classified as follows:

- (a) flocculation and creaming
- (b) coalescence and breaking
- (c) miscellaneous physical and chemical changes
- (d) phase inversion

Creaming and Stokes' Law. Those factors that find importance in the creaming of an emulsion are related by Stokes' law, equation (18-2) (p. 479). The limitations of this equation to actual systems have been discussed previously for suspensions (p. 479), and these apply equally to emulsified systems.

Analysis of the equation shows that if the dispersed phase is less dense than the continuous phase, which is

generally the case in *o/w* emulsions, the velocity of sedimentation becomes negative, that is, an upward *creaming* results. If the internal phase is heavier than the external phase, the globules settle, a phenomenon customarily noted in *w/o* emulsions in which the internal aqueous phase is more dense than the continuous oil phase. This effect may be referred to as *creaming in a downward direction*. The greater the difference between the density of the two phases, the larger the oil globules and the less viscous the external phase, the greater is the rate of creaming. By increasing the force of gravity through centrifugation, the rate of creaming may also be increased. The diameter of the globules is seen to be a major factor in determining the rate of creaming. Doubling the diameter of the oil globules increases the creaming rate by a factor of four.

Example 18-5. Consider an *o/w* emulsion containing mineral oil with a specific gravity of 0.90 dispersed in an aqueous phase having a specific gravity of 1.05. If the oil particles have an average diameter of $5\text{ }\mu\text{m}$ or $5 \times 10^{-4}\text{ cm}$, the external phase has a viscosity of 0.5 poise (0.5 dyne sec/cm^2 or 0.5 g/cm sec), and the gravity constant is 981 cm/sec^2 , what is the velocity of creaming in cm per day?

$$v = \frac{(5 \times 10^{-4})^2 \times (0.90 - 1.05) \times 981}{18 \times 0.5}$$

$$= -4.1 \times 10^{-6}\text{ cm/sec}$$

and since a 24-hour day contains 86,400 sec, the rate of upward creaming, $-v$, is

$$-v = 4.1 \times 10^{-6}\text{ cm/sec} \times 86,400\text{ sec/day} = 0.35\text{ cm/day}$$

The factors in Stokes' equation may be altered to reduce the rate of creaming in an emulsion. The viscosity of the external phase can be increased without exceeding the limits of acceptable consistency by adding a *viscosity improver* or *thickening agent* such as methylcellulose, tragacanth, or sodium alginate. The particle size of the globules may be reduced by homogenization; this, in fact, is the basis for the stability against creaming of homogenized milk. If the average particle size of the emulsion in the example just given is reduced to $1\text{ }\mu\text{m}$ or one fifth of the original value, the rate of creaming is reduced to 0.014 cm per day or about 5 cm per year . Actually, when the particles are reduced to a diameter below $2\text{ to }5\text{ }\mu\text{m}$, Brownian motion at room temperature exerts sufficient influence so that the particles settle or cream slower than predicted by Stokes' law.

Little consideration has been given to the adjustment of densities of the two phases in an effort to reduce the rate of creaming. Theoretically, adjusting the external and internal phase densities to the same value should eliminate the tendency to cream. This condition is seldom realized, however, since temperature changes alter the densities. Some research workers have increased the density of the oil phase by the addition of oil-soluble substances, such as α -bromonaphthalene, bromoform, and carbon tetrachloride, which, however, cannot be used in medicinal products. Mullins and Becker²⁴ added a food grade of a brominated oil to adjust the densities in pharmaceutical emulsions.

Equation (18-2) gives the rate of creaming of a single droplet of the emulsion, whereas one is frequently interested in the rate of creaming at the center of gravity of the mass of the disperse phase. Greenwald³⁵ has developed an equation for the mass creaming rate, to which the interested reader is referred for details.

Coalescence and Breaking. Creaming should be considered as separate from breaking, since creaming is a reversible process, whereas breaking is irreversible. The cream flocules may be redispersed easily, and a uniform mixture is reconstituted from a creamed emulsion by agitation, since the oil globules are still surrounded by a protective sheath of emulsifying agent. When breaking occurs, simple mixing fails to resuspend the globules in a stable emulsified form, since the film surrounding the particles has been destroyed and the oil tends to coalesce. Considerable work has been devoted to the study of breaking instability. The effects of certain factors on breaking are summarized in the following paragraphs.

King³⁶ showed that reduction of particle size does not necessarily lead to increased stability. Rather, he concluded that an optimum degree of dispersion for each particular system exists for maximum stability. As in the case of solid particles, if the dispersion is nonuniform, the small particles wedge between larger ones, permitting stronger cohesion so that the internal phase may coalesce easily. Accordingly, a moderately coarse dispersion of uniform-sized particles should have the best stability. Viscosity alone does not produce stable emulsions; however, viscous emulsions may be more stable than mobile ones by virtue of the retardation of flocculation and coalescence. Viscous or "tacky" emulsifiers seem to facilitate shearing of the globules as the emulsion is being prepared in the mortar, but this bears little or no relationship to stability. Knoechel and Wurster³⁷ have shown that viscosity plays only a minor role in the gross stability of *o/w* emulsions. Probably an *optimum* rather than a *high* viscosity is needed to promote stability.

The *phase-volume ratio* of an emulsion has a secondary influence on the stability of the product. This term refers to the relative volumes of water and oil in the emulsion. As shown in the section on powders (p. 443), uniform spherical particles in loose packing have a porosity of 48% of the total bulk volume. The volume occupied by the spheres must then be 52%.

If the spheres are arranged in closest packing, theoretically they cannot exceed 74% of the total volume regardless of their size. Although these values do not consider the distortions of size and shape and the possibility of small particles lying between larger spheres, they do have some significance with respect to real emulsions. Ostwald³⁸ and others have shown that if one attempts to incorporate more than about 74% of oil in an *o/w* emulsion, the oil globules often coalesce and the emulsion breaks. This value, known as the *critical point*, is defined as the concentration of the internal

phase above which the emulsifying agent cannot produce a stable emulsion of the desired type. In some stable emulsions, the value may be higher than 74% owing to the irregular shape and size of the globules. Generally speaking, however, a phase-volume ratio of 50:50 (which approximates loose packing) results in about the most stable emulsion. This fact was discovered empirically by pharmacists many years ago, and most medicinal emulsions are prepared with a volume ratio of 50 parts of oil to 50 parts of water.

Emulsions can be stabilized by electrostatic repulsion between the droplets, that is, by increasing their zeta potential. Magdassi and Siman-Tov³⁹ used lecithin to stabilize perfluorocarbon emulsions, which appear to be a good blood substitute. Lecithin is a mixture of phospholipids having a negative charge at physiologic pH. The stabilizing effect is due to the adsorption of lecithin at the droplet surface, which creates a negative charge and consequently electrostatic repulsion. Lecithin produces very stable emulsions of triglyceride acids in water for intravenous administration. However, the stability of these emulsions may be poor because in clinical practice they are mixed with electrolytes, amino acids, and other compounds for total parenteral nutrition. The addition of positively charged species such as sodium and calcium ions or cationic amino acids—the charge on the latter depending on the pH—reduces the zeta potential and may cause flocculation. Johnson et al.⁴⁰ studied the effect of heparin and various electrolytes, frequently used clinically, on the stability of parenteral emulsions. Heparin, an anticoagulant, is a

negatively charged polyelectrolyte that causes rapid flocculation in emulsions containing calcium and lecithin. The critical flocculation concentration occurs at a specific zeta potential. The value of this zeta potential can be determined by plotting the flocculation rate against the surface potential and extrapolating to zero flocculation rate.⁴¹ Johnson et al.⁴⁰ explained the destabilizing effect of heparin as follows. Divalent electrolytes such as calcium bind strongly to the surface of droplets stabilized with lecithin to form 1:2 ion-lipid complexes. This causes a charge reversal on the droplets, leading to positively charged particles. The droplets are then flocculated by a bridging of the negatively charged heparin molecules across the positively charged particles, as depicted in Figure 18-10.

When the oil particles, which usually carry a negative charge, are surrounded in an *o/w* emulsion by a film of emulsifier, particularly a nonionic agent, the electrokinetic effects are probably less significant than they are in suspensions in maintaining the stability of the system. The effect of electrolytes in these systems has been studied by Schott and Royce.⁴² Probably the most important factors in the stabilization of an emulsion are the physical properties of the emulsifier film at the interface. To be effective, an emulsifier film must be both tough and elastic and should form rapidly during emulsification. Serrallach et al.⁴³ have measured the strength of the film at the interface. They found that a good emulsifying agent or emulsifier combination brings about a preliminary lowering of the interfacial tension to produce small uniform globules and forms

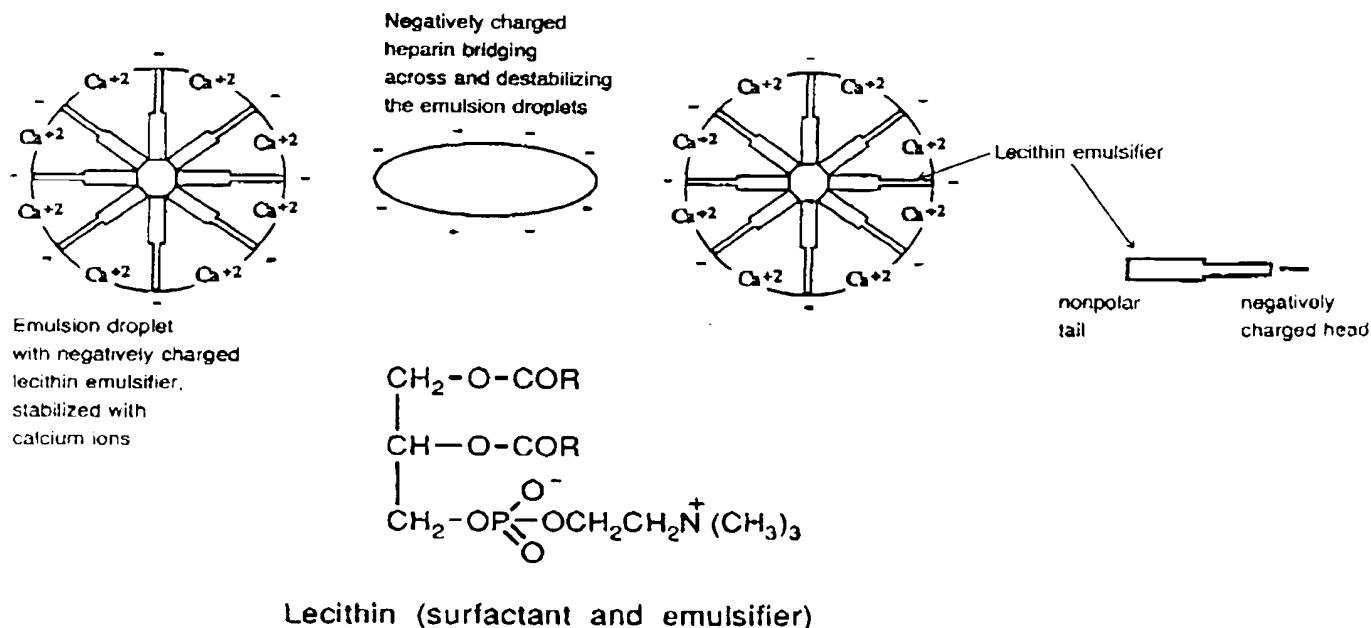


Fig. 18-10. Parenteral emulsion droplets in the presence of the negatively charged emulsifier lecithin, and stabilized by electrostatic repulsion by calcium ions. The emulsion may be flocculated and destabilized by the bridging effect of heparin, a negatively charged polyelectrolyte, which overcomes the stabilizing electrostatic repulsion of the Ca^{2+} ions. (From O. L. Johnson, C. Washington, S. S. Davis and K. Schaupp, *Int. J. Pharm.* 53, 237, 1989, reproduced with permission of the copyright owner.)

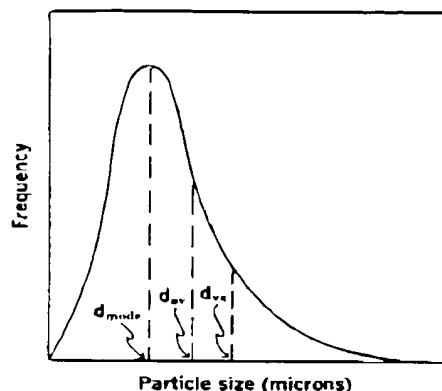


Fig. 18-11. Particle size distribution of an emulsion. Such curves ordinarily are skewed to the right as shown in the figure, and the mode diameter, i.e., the highest point on the curve or the most frequent value, is seen to occur at the lower end of the scale of diameters. The arithmetic mean diameter d_{av} will be found somewhat to the right of the mode in a right skewed distribution and the mean volume-surface diameter d_v is to the right of the arithmetic mean.

rapidly to protect the globules from reaggregation during manufacture. The film then slowly increases in strength over a period of days or weeks.

Evaluation of Stability. According to King and Mukherjee,⁴⁴ the only precise method for determining stability involves a size-frequency analysis of the emulsion from time to time as the product ages. For rapidly breaking emulsions, macroscopic observation of separated internal phase is adequate, although the separation is difficult to read with any degree of accuracy. In the microscopic method, the particle diameters are measured, and a size-frequency distribution of particles ranging from 0.0 to 0.9 μm , 1.0 to 1.9 μm , 2.0 to 2.9 μm , etc., is made as shown in Figure 18-11. The particle size or diameter of the globules in micrometers is plotted on the horizontal axis against the frequency or number of globules in each size range on the vertical axis. Finkle et al.⁴⁵ were probably the first workers to use this method to determine the stability of emulsions. Since that time, many similar studies have been made. Schott and Royce⁴⁶ showed that the experimental problems involved in microscopic size determinations are Brownian motion, creaming, and field flow. Brownian motion affects the smallest droplets, causing them to move in and out of focus so that they are not consistently counted. Velocity of creaming is proportional to the square of the droplet diameter, and creaming focuses attention on the largest droplets because they move faster toward the cover glass than do smaller ones. *Field flow* is the motion of the entire volume of emulsion in the field due to the pressure exerted by the immersion objective on the cover glass, evaporation of the continuous phase, or convection currents resulting from heating by the light source. These workers⁴⁶ described an improved microscopic technique that overcomes these experimental problems and gives a more accurate measure of the droplet size.

An initial frequency distribution analysis on an emulsion is not an adequate test of stability, since stability is not related to initial particle size. Instead, one should perhaps consider the coalescence of the dispersed globules of an aging emulsion, or the separation of the internal phase from the emulsion over a period of time. Boyd et al.,³¹ however, deemed this

method unsatisfactory since the globules may undergo considerable coalescence before the separation becomes visible. These workers conducted particle size analyses with a Coulter centrifugal photosedimentometer. Mean volume diameters were obtained, and these were converted to number of globules per milliliter. King and Mukherjee⁴⁴ determined the specific interfacial area, that is, the area of interface per gram of emulsified oil, of each emulsion at successive times. They chose the reciprocal of the decrease of specific interfacial area with time as a measure of the stability of an emulsion.

Other methods used to determine the stability of emulsions are based on accelerating the separation process, which normally takes place under storage conditions. These methods employ freezing, thaw-freezing cycles, and centrifugation.

Merrill⁴⁷ introduced the centrifuge method to evaluate the stability of emulsions. Garrett, Vold, and others⁴⁸ have used the ultracentrifuge as an analytic technique in emulsion technology. Coulter counting (p. 434), turbidimetric analysis, and temperature tests have also been used in an effort to evaluate new emulsifying agents and to determine the stability of pharmaceutical emulsions. Garti and Magdassi⁴⁹ developed a method to evaluate the stability of oil-water viscous emulsions (ointments and cosmetic creams) containing nonionic surfactants. The method is based on electrical conductivity changes (see pp. 127-128 for conductivity) during nondestructive short heating-cooling-heating cycles. Conductivity curves are plotted during the temperature cycling. A stability index is defined as Δ/h , where h is the change in the conductivity between 35° and 45° C and Δ is the conductivity interval within the two heating curves at 35° C, as shown in Figure 18-12. The *stability index* indicates the relative change in conductivity between two cycles. The smaller the conductivity, the greater is the stability of the emulsion. The method was applied in a series of emulsions at different HLB's, emulsifier concentrations, and oil phase concentrations. The authors reviewed earlier work on electrical conductivity of emulsions as related to stability.

Phase Inversion. When controlled properly during the preparation of an emulsion, phase inversion often results in a finer product, but when it gets out of hand during manufacturing or is brought about by other factors after the emulsion is formed, it can cause considerable trouble.

An *o/w* emulsion stabilized with sodium stearate can be inverted to the *w/o* type by adding calcium chloride to form calcium stearate. inversion may also be produced by alterations in phase-volume ratio. In the manufacture of an emulsion, one can mix an *o/w*

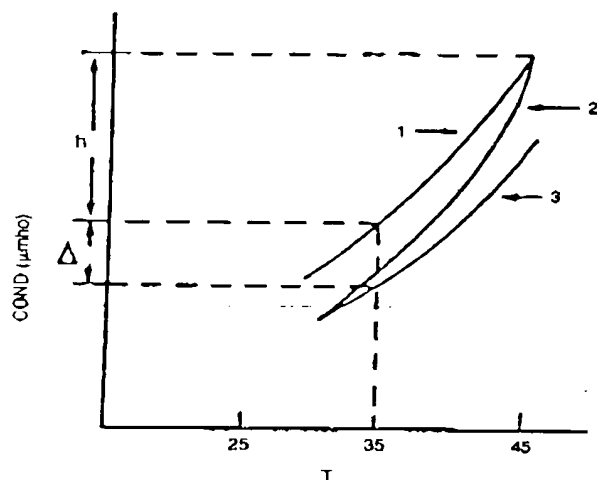


Fig. 18-12. A conductivity versus temperature plot involving successively (1) heating, (2) cooling, and (3) heating. (From N. Garti and S. Magdaassi, *Drug Dev. Ind. Pharm.* 8, 475, 1982, reproduced with permission of the copyright owner.)

emulsifier with an oil and then add a small amount of water. Since the volume of the water is small compared with the oil, the water is dispersed by agitation in the oil even though the emulsifier preferentially forms an oil-in-water system. As more water is slowly added, the inversion point is gradually reached and the water and emulsifier envelope the oil as small globules to form the desired *o/w* emulsion. This procedure is sometimes used in the preparation of commercial emulsions, and it is the principle of the *Continental method* used in compounding practice. The preparation of emulsions is discussed in books on general pharmacy and on compounding and dispensing.

PRESERVATION OF EMULSIONS

While it is not always necessary to achieve sterile conditions in an emulsion, even if the product is for topical or oral use, certain undesirable changes in the properties of the emulsion can be brought about by the growth of microorganisms. These include physical separation of the phases, discoloration, gas and odor formation, and changes in rheologic properties.⁵⁰ Emulsions for parenteral use obviously must be sterile.

The propagation of microorganisms in emulsified products is supported by one or more of the components present in the formulation. Thus, bacteria have been shown to degrade nonionic and anionic emulsifying agents, glycerin, and vegetable gums present as thickeners, with a consequent deterioration of the emulsion. As a result, it is essential that emulsions are formulated to resist microbial attack by including an adequate concentration of preservative in the formulation. Given that the preservative has inherent activity against the type of contamination encountered, the main problem is

obtaining an adequate concentration of preservative in the product. Some of the factors that must be considered to achieve this end are presented here.

Emulsions are heterogeneous systems in which partitioning of the preservative will occur between the oil and water phases. In the main, bacteria grow in the aqueous phase of emulsified systems, with the result that a preservative that is partitioned strongly in favor of the oil phase may be virtually useless at normal concentration levels because of the low concentration remaining in the aqueous phase. The phase-volume ratio of the emulsion is significant in this regard. In addition, the preservative must be in an un-ionized state to penetrate the bacterial membrane. Therefore, the activity of weak acid preservatives decreases as the pH of the aqueous phase rises. Finally, the preservative molecules must not be "bound" to other components of the emulsion since the complexes are ineffective as preservatives. Only the concentration of free, or unbound, preservative is effective. These points have been discussed in some detail in earlier sections of the text. The distribution of solutes between immiscible solvents was presented in Chapter 10, and the preservative action of weak acids in oil-water systems was introduced on page 240. Binding of molecules was discussed in Chapter 12, and the student should consult that chapter for information regarding the types of interaction that are possible between preservative molecules and the components of emulsions, such as nonionic surfactants. In addition to partitioning, ionization, and binding, the efficacy of a particular preservative is also influenced by emulsion type, nutritive value of the product, degree of aeration, and type of container used. These factors are discussed by Wedderburn.⁵⁰

RHEOLOGIC PROPERTIES OF EMULSIONS

Emulsified products may undergo a wide variety of shear stresses during either preparation or use. In many of these processes, the flow properties of the product will be vital for the proper performance of the emulsion under the conditions of usage or preparation. Thus, spreadability of dermatologic and cosmetic products must be controlled to achieve a satisfactory preparation. The flow of a parenteral emulsion through a hypodermic needle, the removal of an emulsion from a bottle or tube, and the behavior of an emulsion in the various milling operations employed in the large-scale manufacture of these products all indicate the need for correct flow characteristics. Accordingly, it is important for the pharmacist to appreciate how formulation can influence the rheologic properties of emulsions.

The fundamentals of rheology have been discussed in Chapter 17. Most emulsions, except dilute ones, exhibit non-Newtonian flow, which complicates interpretation of data and quantitative comparisons between different systems and formulations. In a comprehensive review,